



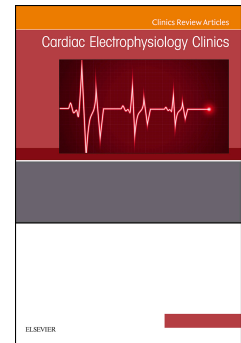
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## Prevalence and Clinical Implications of COVID-19 Myocarditis

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## Prevalence and Clinical Implications of COVID-19 Myocarditis

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**Key Words:** COVID-19, myocarditis, myocardial damage, arrhythmias, vascular damage, Sars-CoV2.

**Key Points:**

- Cardiac involvement is frequent in COVID-19 patients and myocarditis represents one of the most recurrent clinical manifestation.
- Pathophysiology of myocarditis is still understood; direct viral damage or cell-mediated cytotoxicity are the two likely mechanisms.
- Cardiac Magnetic Resonance represents the most important diagnostic tool and diffuse edema may be considered the only CMR hallmark of COVID-19 myocarditis.
- The management of COVID-19 myocarditis is firstly finalized to provide supportive care for heart failure and prevention of lethal cardiac arrhythmias.

**Synopsis**

The clinical manifestations of COVID-19 are widely variable and may involve several districts. Although the clinical course is mostly characterized by respiratory involvement, up to 30% of hospitalized patients have evidence of myocardial injury due to acute coronary syndrome, cardiac arrhythmias, myocarditis, and cardiogenic shock. In particular, myocarditis

is a well-recognized severe complication of COVID-19 and is associated with fulminant cardiogenic shock and sudden cardiac death. The pathophysiology of cardiac injury remains poorly understood and the management and outcomes of myocarditis are not yet clarified. Our aim is to present a comprehensive review about COVID-19 related myocarditis, including clinical characteristics, diagnostic workup, and management.

**Abbreviations.**

ACE: Angiotensin Converting Enzyme 2.

ARB: Angiotensin Receptor Blockers.

ARNi: Angiotensin Receptor-Neprilysin Inhibitors.

CMR: Cardiac Magnetic Resonance.

COVID-19: Coronavirus Disease 2019.

ECG: Electrocardiogram.

EMB: Endomyocardial Biopsy.

HF: Heart Failure.

IL-6: Interleukin-6.

IVIG: Intravenous Immunoglobulins.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

## Introduction

In December 2019 the first case of coronavirus disease 2019 (COVID-19) was described in Wuhan, China, in a patient complaining of flu-like symptoms [1]. The pathogen has been recognized as a novel enveloped RNA  $\beta$ -coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The clinical manifestations of COVID-19 are widely variable ranging from asymptomatic infection to multi-organ failure and death. Although the clinical course of SARS-CoV-2 infection is mostly characterized by respiratory involvement, ranging from mild influenza-like illness to acute respiratory distress syndrome, it soon became evident that COVID-19 affects multiple organ systems, including the cardiovascular system [2–4]. Overall, up to 30% of hospitalized patients have evidence of myocardial injury which is associated with a greater need for mechanical ventilatory support and higher in-hospital mortality [5,6]. Cardiovascular manifestations include acute coronary syndrome, atrial and ventricular arrhythmias, myocarditis, and cardiogenic shock [3]. In particular, myocarditis is a well-recognized severe complication of COVID-19 and is associated with fulminant cardiogenic shock and sudden cardiac death [7–9]. The pathophysiology of cardiac injury remains poorly understood and the management and outcomes of myocarditis are not yet clarified. Thus, we present a comprehensive review about COVID-19 related myocarditis, describing clinical characteristics, diagnostic workup, and management.

## Epidemiology of COVID- 19- related myocarditis

The annual incidence of acute myocarditis from all causes is approximately 22 cases per 100,000 population, with heart failure (HF) occurring in 0.5% to 4.0% of these cases [10]. The true prevalence of myocarditis among COVID-19 patients is difficult to establish, because the early reports often lacked the specific diagnostic modalities to assess myocarditis and the circulating biomarkers reflecting myocardial injury can also be related to non-primary

myocardial damage (multi organ failure, hypoxia, hypo-perfusion and activation of hemostasis) [11].

Overall, several studies report that myocardial injury occurs in 15–27.8% of severe COVID-19 pneumonia cases [12–14]. Additionally, COVID-19 related myocarditis are also described in patients without prior pneumonia indicating the probability of late onset of cardiovascular complications, even in those with mild symptoms [15,16]. Otherwise, diffuse myocardial injury was also detected in the early stage of COVID-19 recovered patients who had no active cardiac symptoms [17].

### **Immunological and pathophysiological mechanisms**

SARS-CoV-2 is a  $\beta$ -coronavirus whose genome consists of single-stranded RNA with positive polarity that belongs to the Coronaviridae family. The virus invades the human host cell by binding with high affinity to the angiotensin converting enzyme 2 (ACE 2) receptor. ACE2 can be found on the ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes, and cardiomyocytes. Therefore, this mechanism appears to be the pathway of SARS-CoV-2 infection of the human heart, especially in case of HF as ACE2 is upregulated [18]. After penetration, viral RNA enters the cell nucleus for replication inducing human immunological response to the virus [19].

The mechanism of heart damage remains poorly understood and several mechanisms have been proposed to explain the underlying pathophysiology of COVID-19-related acute myocarditis [20]. Among them, the main theories are the following (Figure 1):

- a) *Myocardial damage due to the direct viral action.* SARS-CoV-2 invades cells by binding to ACE-2 receptors, that are expressed in human myocardium [21]. Despite that nowadays is still unclear if SARS- CoV- 2 is directly associated to cardiomyocyte infection and damage.

Indeed, although myocarditis has been clearly recognized at endomyocardial biopsy (EMB) or autopsy, there is no current evidence of myocarditis directly produced by cardiomyocyte infection due to the SARS-CoV-2 in humans [8,22–24] and the associated lymphocytic myocarditis may be related to the inflammatory reaction induced by cytokines [25], or by extrapulmonary migration of infected alveolar macrophages.

- b) *Via cell-mediated cytotoxicity.* Activated CD8 T lymphocytes migrate to the heart and cause myocardial inflammation, inducing the cytokine release syndrome, a severe inflammatory response resulting in hypoxia and apoptosis of cardiomyocytes. This cytokine storm is proposed as the main mechanism underlying COVID-19-induced acute fulminant myocarditis [21,26]. Substantial evidence suggest that elevated serum level of interleukin (IL)-6 is present in COVID-19 patients, especially in those with severe presentations [27]. As matter of fact, IL-6 seems to be the central mediator of cytokine storm, in which it coordinates the proinflammatory responses from immune cells, including the T-lymphocytes [28]. This process causes T-lymphocyte activation and a further release of inflammatory cytokines, which stimulate more T-lymphocytes, leading to a positive feedback loop of immune activation and myocardial damage [29]. Furthermore, IL-6 might cause a displacement of plakoglobin, a desmosomal protein, that could be arrhythmogenic due to the deposition of fibrous tissue [30].
- c) *interferon-mediated hyperactivation* of the innate and adaptive immune system has also been proposed, especially in pediatric myocarditis COVID-19 related [31].

Most probably, as proposed by Esfandiarei et al. the pathophysiology of viral myocarditis is a miscellaneous of direct viral cell injury and T-lymphocyte-mediated cytotoxicity, which can be augmented by the cytokine storm syndrome [32]. Furthermore, cardiotoxic anti-viral

therapies may play a role in the genesis of myocardial inflammation and a drug-induced myocarditis should also be considered [33,34].

### **Clinical presentation**

Clinical presentation of SARS-CoV-2 myocarditis could be very different: some patients may present relatively mild symptoms, such as fatigue and dyspnea, while others may complain of chest pain or chest tightness [15,20]. Otherwise, many patients show symptoms of tachycardia and acute-onset HF until to cardiogenic shock or sudden cardiac death [35–38]. The early signs of fulminant myocarditis usually look like those of sepsis: hyperpiesia with low pulse pressure, cold or mottled extremities, and sinus tachycardia. Fulminant myocarditis are also frequently associated with ventricular arrhythmias because massive myocardial necrosis may generate some micro re-entry circuits and induce an electrolyte imbalance that trigger malignant tachycardia [39–41]. Overall, cardiac arrhythmias are frequently in COVID-19 patients affected by myocarditis: several studies reported an incidence of cardiac arrhythmias between 15-20% [42,43]. The exact nature of the arrhythmias was not clearly reported but it has been speculated that their possible pathophysiology could be include: direct injury to cardiomyocytes and conduction system, ischemia from microvascular disease, re-entrant arrhythmias due to myocardial fibrosis or scars, proinflammatory cytokines predisposing to arrhythmogenicity (Figure 2) [19,41,44].

### **Diagnosis**

In COVID-19 patients, the criteria for the diagnosis of myocarditis are the same as in the other patients. However, the diagnostic pathway may be different because it is conditioned, first of all, by the need to protect all health care operators from the risk of SARS-CoV-2 infection [45]. In Figure 3 we provide a flow-chart for the diagnosis of COVID-19 myocarditis, considering Troponin assessment as first step in the diagnostic work up, since it

can be easily performed and its level is usually elevated in COVID-19-related myocarditis [6,15]. However, even in presence of normal Troponin if clinical suspicion of myocarditis is strong cardiologic exams should be performed. A fundamental step in the diagnostic process is the exclusion of obstructive coronary artery disease since high troponin level could be the result of exacerbation of patient's subclinical coronary artery disease due to inflammatory state, which increases cardiac oxygen demand. The oxygen supply-demand mismatch could in turn precipitate ischemia, resulting in type 2 myocardial infarction [38,46,47].

Electrocardiographic (ECG) changes are not pathognomonic in myocarditis, since a variety of ECG patterns from sinus tachycardia and ectopic beats to ST elevation and T-wave inversion have been described [48–50]. Other ECG abnormalities, including new-onset bundle branch block, QT prolongation, pseudo infarct pattern, and bradyarrhythmia with advanced atrioventricular nodal block, can be observed in myocarditis.

Transthoracic echocardiography is the first imaging technique performed and can be coupled with pulmonary ultrasound evaluation [51]. Global and regional ventricular systolic dysfunctions are not specific markers of acute myocarditis: ventricular dysfunction could be due to several other cardiac diseases and, on the other hand, patients with myocarditis may have a normal left ventricular function. In addition, the possibility of a pre-existing ventricular dysfunction should be always taken into consideration, especially if the patient has known cardiovascular risk factors. Echocardiography also has prognostic implications; patients with marked reduction in right ventricular function have an increased risk of death [52].

Thus, in patients with elevated troponin the presence of normal ECG and echocardiogram cannot exclude completely a COVID-19 myocarditis and a close cardiologic follow-up should be performed.

Cardiac magnetic resonance (CMR) should be always performed in case of abnormal ECG and/or echocardiogram and the findings should be interpreted according to the revised Lake

Louise consensus criteria [53,54]. In clinically stable patients, both CMR and coronary computed tomography could be theoretically performed for myocarditis diagnosis in a radiology section dedicated to COVID-19 patients. CMR is used in COVID-19 patients to assess biventricular function, the pattern of edema and inflammation within the myocardium, and the presence of pericardial involvement. The common imaging findings on CMR included increased T1 and T2 mapping values and edema on T2/STIR sequences [55]. Diffuse edema may be considered the only CMR hallmark of COVID-19 myocarditis because LGE may be completely absent or minimal, revealing unremarkable myocyte necrosis [56]. LGE was seen in less than half of the patients and if present, LGE was detected in the subepicardial location [55]. The presence of biventricular dysfunction, the detection of patchy, mid-wall, septal or inferior LGE enhancement, and its persistence over three months have been associated with adverse cardiac events including sudden cardiac death and heart transplantation [57–59].

In selected cases with CMR suggestive for myocarditis an EMB may be performed. The consensus paper from the American Heart Association/American College of Cardiology recommended EMB preferably in new onset HF with hemodynamic instability or in life-threatening arrhythmias to establish the specific therapy [60,61]. Although EMB is definitive for the diagnosis, is rarely used in COVID-19 patients probably to limit spread of the infection to medical workers. When performed, the EMB showed scattered myocyte necrosis and CD4 and CD8 lymphocytes near vascular structures in patients with mild troponin elevation [62][55], whereas patients with more severe clinical presentations had interstitial inflammation and vasculitis of intramural vessels represented by T-lymphocytes and CD68+ macrophages, associated to foci of necrosis (figure 4, Panel A-B). The macrophage infiltration was seen to correlate with the elevated systemic levels of proinflammatory cytokines. While coronary involvement was uncommon, endothelitis was commonly encountered because virus showed tropism for endothelial cells [36,63].

## **Treatment**

The management of COVID-19 myocarditis is firstly finalized to provide a comprehensive management of HF [64]. However, a prompt treatment of respiratory symptoms aiming to promote viral clearance may have an additional benefit of reducing subsequent cardiovascular complications.

### *Management of Heart Failure*

Patients that develop HF from COVID-19 myocarditis should be treated with guideline-directed medical therapy, including ACE inhibitors, angiotensin receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitors (ARNi), beta blockers and diuretics [65]. Due to their mechanism of action, there was initial concern that treating COVID-19 patients with ACEi, ARB and ARNi would worsen clinical outcomes. Thus, several recent observational studies showed that there was no significant difference between patients treated with ACEi or ARB and those that discontinue these medications and, therefore, is generally recommended to initiate or continue these drugs during and beyond the disease [66,67].

In patients with fulminant myocarditis and cardiogenic shock, in the acute phase is recommended the administration of inotropes and/or vasopressors and in the longer-term may be required mechanical circulatory support [68].

Appropriate management of cardiac arrhythmias related to COVID-19 myocarditis is crucial in mitigating patient's adverse health outcomes. Bradyarrhythmia may require temporary cardiac pacing, while tachyarrhythmias may respond to antiarrhythmic drugs. Beta blockers may be considered for hemodynamically stable patients whereas amiodarone is typically administered in the critically ill, although it can prompt QTc prolongation, especially when combined with azithromycin or hydroxychloroquine [69–71]. Alternatively, lidocaine infusion or oral flecainide may be considered [72–74].

### *SARS-CoV-2 Viral Therapies*

Therapies for SARS-CoV-2 have focused primarily on restoration of respiratory function and there are little data to define therapeutic options in COVID-19 myocarditis. Different anti-viral therapies were expected to be effective in hospitalized patients with COVID-19: remdesivir, hydroxychloroquine and interferon beta- 1a. Unfortunately, all these drugs had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay [75,76]. Moreover, many pharmacological agents used empirically to treat COVID-19, especially hydroxychloroquine, may expose patients to an increased risk of cardiac arrhythmias: indeed, hydroxychloroquine, may cause QTc interval prolongation and its combination therapy with macrolides should be accompanied by QTc interval monitoring [77].

Nonsteroidal anti-inflammatory drugs are generally not indicated in myocarditis patients because they are the known cause of renal impairment and sodium retention, which could exacerbate acute ventricular dysfunction [68].

Since cytokine release syndrome is a probable mechanism of injury in COVID-19 myocarditis, some authors suggested to use anti-inflammatory and anti-cytokine drugs like high-dose steroids and intravenous immunoglobulins (IVIG) [78]. However, the use of high-dose steroids in COVID-19 patients has given conflicting results: if in a retrospective study there was an improvement of survival, another trial showed a reduction in viral clearance, increased risk of over infection and mortality for all causes [79–81]. Overall, in patients hospitalized with COVID-19 the use of corticosteroid resulted in a clinical benefit only in those who were receiving invasive mechanical ventilation and oxygen therapy [82].

Regarding purified IVIG, they gave encouraging result in a small group of five critical COVID-19 patients without clinically suspected myocarditis but no additional evidence exists in patients with COVID-19 established myocarditis [83]. The immunomodulatory effects of

IVIG are multifactorial showing not only anti-viral effects, but also anti-inflammatory effects by suppressing inflammatory cytokines [84]. Currently, the evidence does not support the routine use of IVIGs alone.

Several immune therapies have also been investigated and agents targeting IL-6, such as tocilizumab, have also been evaluated in the REMAP-CAP study showing promising results in critically ill patients [85].

In summary, in patients with isolated SARS-CoV-2 myocarditis who are hospitalized, or hypoxemic, high-dose steroids may be reasonable while should be avoided in patients with less severe illness. Regarding targeted immunomodulatory therapy with IL-6 antagonists, additional data are needed to establish whether it can be recommended for SARS-CoV-2 myocarditis.

## **Prognosis**

Although there are very limited data about the clinical outcomes of COVID-19 myocarditis, it seems that most patients have a favorable prognosis [56,86]. It should also be underlined the complexity of the COVID-19 and the possibility to die for other reasons than cardiac involvement (acute severe respiratory distress, systemic embolism, multiorgan failure).

Overall, Shi et al. reported that patients with myocardial injury presented higher mortality rate than those without myocardial injury (51.2% vs. 4.5%;  $p < 0.001$ ), being an independent risk factor for mortality [12]. In addition, myocardial injury was associated with a higher incidence of severe respiratory distress (58.5% vs. 14.7%), need of non-invasive (46.3% vs. 3.9%) or invasive ventilation (22.0% vs. 4.2%), and complications such as acute kidney injury (8.5% vs. 0.3%) and coagulopathy (7.3% vs. 1.8%) [12]. Also, patients with an increase of troponin present higher levels of leukocytes, D-dimer, ferritin, and IL-6, portraying an important correlation between myocardial injury and inflammatory hyperactivity triggered by

the viral infection. Raised troponin levels in COVID-19 are associated with worse outcome, but the specific prognostic role of myocarditis is unknown [87].

In general, myocardial involvement in COVID-19 is associated with an increased mortality, but isolated myocarditis is not necessarily a marker of poor prognosis. However, given the paucity of published data and the inhomogeneity of the cases, conclusive assertion on prognosis cannot be made.

## **Conclusions**

Myocarditis is a common complication of COVID-19 infection. Direct viral damage or cell-mediated cytotoxicity are the two likely pathophysiological mechanisms. Although CMR represents the most important diagnostic tool because diffuse edema may be considered the only CMR hallmark of COVID-19 myocarditis, the definitive diagnosis of myocarditis is obtained via EMB. Treatment of myocarditis should be based on therapy for ventricular dysfunction and clinical status, including arrhythmias and HF, while high-dose steroids should be reserved to more compromised patients. Myocardial involvement in COVID-19 is associated with an increased mortality, but isolated myocarditis is not necessarily a marker of poor prognosis.

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**FIGURE LEGENDS**

**Figure 1. Physiopathogenesis and clinical presentation of COVID-19 myocarditis.**

**Figure 2. Possible mechanism of arrhythmogenesis in COVID-19 myocarditis.**

**Figure 3. Proposed flow-chart for the diagnosis of COVID-19 myocarditis.** *CAD: Coronary Artery Disease; CMR: Cardiac Magnetic Resonance; COVID-19: Coronavirus Disease 2019; CTA: Computed Tomography Angiography; EMB: Endomyocardial Biopsy; PCI: Percutaneous Coronary Intervention.*

**Figure 4. Left ventricular endomyocardial biopsy of a patient with COVID-19 myocarditis.**

**Panel A.** Focal active myocarditis depicted by lymphomononuclear infiltrated (arrows) with necrosis of the adjacent cardiomyocytes (Hematoxylin Eosin 10X magnification). **Panel B.** Myocarditis was associated with vasculitis of intramural vessels (Hematoxylin Eosin 20X magnification).

## COVID-19 Myocarditis

| Potential Mechanisms          |  |
|-------------------------------|--|
| 1. Direct Viral Action        | Myocardial damage due to the direct viral action or to extrapulmonary migration of infected alveolar macrophages       |
| 2. Cell-mediated cytotoxicity | Lymphocytes migrate to cardiomyocytes and cause inflammation of the myocardium, inducing the cytokine release syndrome |
| 3. Interferon hyperactivation | Interferon stimulates hyperactivation of the innate and adaptive immune system   |

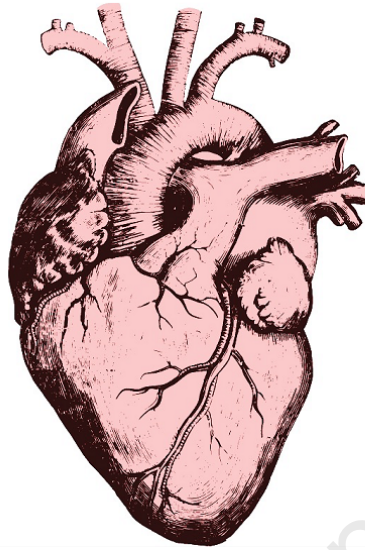
  

| Clinical Presentation |                    |                                |                              |
|-----------------------|--------------------|--------------------------------|------------------------------|
| <b>ASYMPTOMATIC</b>   | <b>ARRHYTHMIAS</b> | <b>ACUTE HEART<br/>FAILURE</b> | <b>CARDIOGENIC<br/>SHOCK</b> |

## Possible mechanism of arrhythmogenesis in COVID-19 myocarditis

### ACUTE

- Cardiomyocyte injury
- Pericardial inflammation
- Microvascular ischemia



### CHRONIC

- Post-inflammatory fibrosis or scarring
- Pro-inflammatory cytokines may cause gap junction's disfunctions

